REMARKS

Claims 36, 39-43, 47, 57, 59, 60, and 89-97 are pending. Claims 89-91 were rejected under 35 U.S.C. § 112, first paragraph, and claims 36, 39-43, 47, 57, 59, 60, and 92-97 were rejected under 35 U.S.C. § 103(a).

Support for the claim amendments

Claim 36 has been amended to incorporate the features of cancelled claims 39 and 40 and now refers to isolated cells or tissue, support for which may be found, for example, on page 12, lines 24-30. In addition, claims 36, 59, and 60 are now drawn to transplantable compositions for use in humans comprising a cell or tissue having an HLA class I surface antigen. Such cells and tissues are described throughout the specification, for example, on page 12, lines 24 to 26, and page 17, lines 12 to 25. Furthermore, claim 41 has been amended to correct claim dependency. No new matter has been added by these amendments.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 89-91 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification fails to provide an enabling disclosure or an adequate written description of the invention, and also fails to present the best mode for carrying out the invention.

Turning to the first ground of rejection, the current Office Action asserts that the specification lacks guidance as to making and using a genetically-engineered cell. Applicant believes that this basis for the enablement rejection is unfounded.

On this point, the Examiner is directed to the specification, for example, at pages 10-12. There Applicant provides methods and published references disclosing techniques useful for genetically engineering cells having decreased class I expression. For example, under the heading of "Transgenic Animals with

Decreased HLA Class I Expression," beginning on page 10, line 3, Applicant states

> As an alternative or an adjunct to masking surface antigens on cells of donor tissues prior to transplantation, such tissues can be grown in transgenic animals which have been genetically altered so that surface antigen expression is diminished. Such transgenic animals can be made by standard transgenic techniques, employing genes which delete or inactivate the gene encoding the target antigen, or delete or inactivate a gene necessary for its expression on the cell surface, by homologous recombination. For example, in the case of HLA class I expression, homologous recombination can be used either to delete or inactivate the HLA class I molecule itself, or to inactivate or delete a companion molecule necessary for its surface expression, * * *.

Applicant further states at page 10, lines 21-25

> Inhibition of class I expression on the surfaces of cells, e.g., islet cells, can thus be achieved either by deletion or inactivation of one of the HLA class I chains, or by deletion or inactivation of the carrier β-2 microglobulin molecule, * * *.

Applicant also states, under the heading "*In Vitro* Methods to Decrease HLA Class I Expression," beginning on page 11, line 5, that

> Transfection of cultured kidney cells with fragments of adenovirus causes elimination of surface HLA class I antigenic expression, * * *.

Furthermore, under the heading "Local Blockage of Recipient T-Cell Receptors with Secreted Donor Antigens," beginning on page 11, line 28, Applicant states that

> [I]n the case of donor tissue containing parenchymal cells bearing surface HLA class I antigen, rather than masking the antigen, those cells can be transfected with DNA encoding soluble antigen, which is secreted and which competitively binds to the CD8 receptor on the T-lymphocytes of the recipient which would otherwise bind to the membrane-bound HLA class I antigen on the donor tissue cells. The techniques for carrying out this procedure will be analogous to methods used by other workers to bring about secretion of a recombinant protein in concert with insulin secretion, * * *.

These sections of the specification describe techniques that may be used to successfully genetically manipulate a cell. Disrupting a gene in a cell and transfecting DNA into a cell are clear examples of genetically engineering a cell and these techniques are standard in the art. Furthermore, support for the term "genetically-engineered" may be found on page 19, line 4, of the specification.

Turning to the assertion that Applicant's specification fails to provide an adequate written description of genetically-engineered cells, Applicant notes that the adequate written description requirement of 35 U.S.C. § 112, ¶ 1 provides:

> the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...

The written description requirement serves "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). In order to meet the written description requirement, the applicant need not utilize any particular form of disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Stated another way, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991).

As is stated above, claims 89-91 are drawn to transplantable compositions that include genetically-engineered cells where class I surface antigens have been

masked or partially or fully eliminated. Applicant's specification explicitly describes to the skilled worker what is claimed. For example, as is discussed above, Applicant explicitly describes methods for producing cells that have decreased expression of class I molecules. Clearly, Applicant was in possession of the claimed invention at the time the application was filed and provided a written description that readily enables the skilled worker to produce genetically-engineered cells falling within the claimed subject matter. There can be no question that Applicant's specification conveys clearly to those skilled in the art that the inventor has invented the claimed subject matter. Applicant's specification therefore satisfies the written description requirement of § 112. This rejection may be withdrawn.

The final basis for the present enablement rejection is the contention that, according to the Examiner, Applicant's specification fails to present the best mode contemplated by the Applicant for carrying out the invention. Regarding the requirements for rejection for lack of best mode, the MPEP (§ 2165.03, Rev. 1., February 2000) states that "the examiner should assume that the best mode is disclosed in the application, unless evidence is presented that is inconsistent with that assumption." As is noted above, Applicant's specification not only describes the claimed invention, but also teaches how to make and use the claimed genetically-engineered cells. Moreover, the Office has failed to provide evidence supporting the rejection for lack of best mode. Accordingly, this final basis for the enablement rejection should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 36, 39-43, 47, 57, 59, 60, and 92-97 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Stock *et al.* (*Journal of Surgical Research* 46:317-321, 1989) in view of Faustman *et al.* (*Proc. Natl. Acad. Sci. USA* 78:5156-5159, 1981). This rejection is addressed as follows.

Stock *et al.* describe *in vitro* experiments in which murine pancreatic islet cells were treated with intact anti-class I murine monoclonal antibody and then incubated with murine T-lymphocytes. In addition, Stock *et al.* report, under "Results" on page 319, that "generation of allospecific CTL [cytotoxic T-lymphocytes] was nearly abrogated by anti-MHC class I pretreatment" and go on to suggest, in the last paragraph on page 320, that a "possibility [for preventing rejection] could involve blocking the MHC class I signal with an $F(ab)_2$ fragment of the appropriate anti-MHC class I antibody."

Applicant submits that the claimed invention is not obvious over the Stock *et al.* reference. First, Applicant's discovery that $F(ab)_2$-masked islet cells of one species could be successfully transplanted into an animal of a different, unrelated species without rejection, and with long-term maintenance of function, was totally unexpected and could not have been predicted from Stock *et al.* or any other prior art. Stock *et al.* carried out ***in vitro*** experiments, which, as is well known, frequently fail to be predictive of *in vivo* results. In the *in vivo* world, many factors could have prevented success. For example, nothing in the Stock *et al. in vitro* experiments takes into account the humoral, *i.e.*, B-cell-mediated, immune response known to play a major role in the rejection of transplanted tissue. Before Applicant carried out her experiments, it could not have been predicted that $F(ab)_2$ masking would allow successful, long-term transplantation of foreign tissue into a living animal without humoral immune system-mediated rejection. Applicant found that the $F(ab)_2$-pretreated transplanted tissue was essentially free of adjacent lymphocyte deposits 200 days following transplantation, and further found that the transplanted cells were functional after 200 days. Certainly nothing in Stock *et al.* was predictive of this dramatic result.

Furthermore, even as to the T-lymphocyte response to which Stock *et al.* confine themselves (putting aside other potential *in vivo* problems such as a likely B-cell response), Applicant's results were surprising and unexpected. In the Stock *et al.* experiment, measuring cytolytic T-cell activity was carried out immediately

following the contacting of freshly masked islet cells with lymphocytes. The abrogation of the CTL response was thus measured only in the extreme short-term; one of ordinary skill in the art would have expected that, over time, when the masking antibody dissociated from the islet cells, the CTL response would take place, particularly *in vivo*, where a limitless supply of potential CTLs is available.

Based on the results of the Stock *et al.* experiments, one of ordinary skill in the art would not have expected masking to have succeeded by substituting $F(ab)_2$ fragments for intact antibodies. Stock *et al.* used intact antibodies, which cannot be used *in vivo* because the Fc portion would fix complement and bring about lysis of the transplant. But if one were to have addressed this problem by substituting $F(ab)_2$ fragments for intact antibody molecules, one would have expected to compound the potential problem of antibody dissociating from the transplant, exposing the previously masked antigens to the host's T-lymphocytes. As was well known, $F(ab)_2$ fragments have notoriously low affinities for cell surface antigens, compared to intact antibodies. For example, Winearls *et al.* (*Transplantation* 28:36-39, 1979; copy enclosed) report that $F(ab)_2$ fragments are 100 times less effective than intact IgG in enhancement of graft tolerance, and go on to warn, in the last paragraph on page 39, that "this large difference in potency makes the clinical use of $F(ab)_2$ impractical." Thus the long-term success obtained by Applicant was all the more surprising, as it employed $F(ab)_2$ fragments.

In sum, there could have been no reasonable basis for predicting, based on the Stock *et al. in vitro* experiments using murine cells, that Applicant could successfully implant tissue into a human, and that this tissue would survive and remain functional for a prolonged period of time.

Turning to the Faustman *et al.* reference, Applicant notes that this reference also fails to provide a reasonable basis for predicting the success of the claimed invention. Faustman *et al.* disclose the treatment of islets with anti-MHC class II antibodies and complement prior to transplantation. Unlike the instant invention, which is drawn to the masking of MHC class I antigen on cells, the Faustman *et*

al. reference teaches the removal of MHC class II bearing cells. In Faustman *et al.*, the removal of MHC class II bearing cells was taught to be important to eliminate passenger lymphocyte cells that may be present in the graft. In contrast to MHC class II molecules which are expressed only on lymphoid cells, MHC class I molecules are present on all nucleated cells. Furthermore, the method disclosed in the Faustman et al. reference is directed toward the removal of cells by lysis using antibody and complement. As all cells in the graft express MHC class I molecules, if, instead of whole anti-class II antibodies, whole anti-class I antibodies were used in this method, the entire graft would be lysed. The instant claims are directed to the masking of class I antigens with a non-lytic masking agent that will not result in the lysis and removal of cells. Accordingly, Applicant submits that the method disclosed by Faustman et al. is irrelevant to the claimed invention.

In addition, there was no motivation to combine the teachings of Stock *et al.* and Faustman *et al.* For the reasons presented above, the *in vitro* method employed by Stock *et al.* cannot be used to accurately predict the *in vivo* effectiveness of a treatment. As a matter of fact, Applicant's specification, see for example groups 3 and 4 of Table 1, teaches that the use of whole anti-MHC class I antibodies, such as those used by Stock *et al.*, would be utterly ineffective in an *in vivo* environment. Moreover, the use of the Stock et al. method would result in accelerated rejection *in vivo*. The *in vivo* results taught by Faustman *et al.* are based on an entirely different method of pretreatment, the use of anti-MHC class II antibodies, not anti-MHC class I antibodies, than that presently claimed or that used by Stock *et al.* Consequently, one of ordinary skill in the art would not have been motivated to combine the references in the manner suggested by the Examiner and, thus, the *in vivo* success of Faustman *et al.* could not have been used to predict whether the method of Stock *et al.* would succeed *in vivo*. In view of these arguments, Applicant submits that the § 103 rejection should be withdrawn.

Information Disclosure Statement

Applicant also draws the Examiner's attention to the Information Disclosure Statement mailed on April 19, 2001 and requests that the Form PTO-1449 submitted with that statement be initialed and returned with the next Action.

CONCLUSION

Applicant submits that the claims are in condition for allowance and such action is respectfully requested.

A marked-up version indicating the amendments made to claims 36, 41, 59, and 60, and a clean version of all pending claims reflecting entry of the amendments, are enclosed.

Also enclosed is a petition to extend the period for replying for three months, to and including October 23, 2001.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Version with Markings to Show Changes Made

Cancel claims 39, 40, and 47.

Amend claims 36, 41, 59, and 60.

36. (Three times amended) A transplantable composition for use in humans comprising [a cell] isolated cells or isolated tissue of a type normally bearing [a] an HLA class I surface antigen that causes an immune response against the cell or tissue in a human recipient, wherein the antigen is modified, masked, or has been partially or wholly eliminated to decrease said immune response, such that upon introduction of the composition into a human, lysis of said cell or tissue is prevented; wherein

(a) said class I antigen is masked by contacting said cell or tissue with a masking agent which is capable of forming a complex with said class I antigen on said cell or tissue;

(b) said class I antigen on said cell or tissue is modified by capping; or

(c) said class I antigen on said cell or tissue is partially or wholly eliminated by inhibiting expression of said antigen on said cell or tissue.

41. (Twice amended) The composition of claim [40] 36, wherein the antigen is masked with at least two masking agents.

59. (Three times amended) A transplantable composition for use in humans comprising a cell or tissue of a type normally bearing [a] an HLA class I surface antigen that causes an immune response against the cell or tissue in a human recipient, wherein the antigen is masked such that upon introduction of the composition into a human, lysis of said cell or tissue is prevented.

60. (Three times amended) A transplantable composition for use in humans comprising a cell or tissue and at least one masking agent, wherein the masking

agent binds to [a] an HLA class I surface antigen of the cell or cells comprising the tissue that causes an immune response against the cell or tissue in a human recipient such that upon introduction of the composition into a human, lysis of said cell or tissue is prevented.

Clean Version of all Pending Claims

36. (Three times amended) A transplantable composition for use in humans comprising isolated cells or isolated tissue of a type normally bearing an HLA class I surface antigen that causes an immune response against the cell or tissue in a human recipient, wherein the antigen is modified, masked, or has been partially or wholly eliminated to decrease said immune response, such that upon introduction of the composition into a human, lysis of said cell or tissue is prevented; wherein

(a) said class I antigen is masked by contacting said cell or tissue with a masking agent which is capable of forming a complex with said class I antigen on said cell or tissue;

(b) said class I antigen on said cell or tissue is modified by capping; or

(c) said class I antigen on said cell or tissue is partially or wholly eliminated by inhibiting expression of said antigen on said cell or tissue.

41. (Twice amended) The composition of claim 36, wherein the antigen is masked with at least two masking agents.

42. (Amended) The composition of claim 41, wherein the at least two masking agents are obtained from polyclonal antisera raised against the antigen.

43. (Amended) The composition of claim 36, wherein the cell or tissue has at least two different antigens which are masked with at least two different masking agents.

57. (Amended) The composition of claim 36, which comprises a neuronal cell.

59. (Three times amended) A transplantable composition for use in humans comprising a cell or tissue of a type normally bearing an HLA class I surface antigen that causes an immune response against the cell or tissue in a human recipient, wherein the antigen is masked such that upon introduction of the composition into a human, lysis of said cell or tissue is prevented.

60. (Three times amended) A transplantable composition for use in humans comprising a cell or tissue and at least one masking agent, wherein the masking agent binds to an HLA class I surface antigen of the cell or cells comprising the tissue that causes an immune response against the cell or tissue in a human recipient such that upon introduction of the composition into a human, lysis of said cell or tissue is prevented.

89. The composition of claim 36, wherein said composition comprises a genetically engineered cell.

90. The composition of claim 59, wherein said composition comprises a genetically engineered cell.

91. The composition of claim 60, wherein said composition comprises a genetically engineered cell.

92. The composition of claim 36, wherein the cell is a non-lymphocytic cell.

93. The composition of claim 36, wherein the tissue comprises non-lymphocytic cells.

94. The composition of claim 59, wherein the cell is a non-lymphocytic cell.

95. The composition of claim 59, wherein the tissue comprises non-lymphocytic cells.

96. The composition of claim 60, wherein the cell is a non-lymphocytic cell.

97. The composition of claim 60, wherein the tissue comprises non-lymphocytic cells.